

Claims:

1. A method for forming matrix stabilized enzyme crystals comprising the step of cross-linking a crystalline enzyme with at least one polymer having one or more reactive moieties effective to adhere to the crystal layer of the crystalline enzyme using a multi-functional cross-linking reagent in an amount sufficient to form said matrix stabilized enzyme crystals which are resistant to degradation by proteolytic enzymes.
2. The method of claim 1 wherein the enzyme is selected from the group consisting of phenylalanine ammonia lyase, L-methionine- γ -lyase, lipases, and carboxypeptidase-A.
3. The method of claim 1, wherein the enzyme is phenylalanine ammonia lyase.
4. The method of claim 1 wherein the multi-functional cross-linking reagent is a dialdehyde cross-linking reagent.
5. The method of claim 4 wherein the dialdehyde cross-linking reagent is a linear or branched dialdehyde.
6. The method of claim 4 wherein the dialdehyde cross-linking reagent is selected from the group consisting of substituted or unsubstituted glutaraldehyde (1,5-Pentanedial), malonaldehyde (1,3-Propanedial), succinaldehyde (1,4-Butanedial), adipaldehyde (1,6-Hexanedial), pimelaldehyde (1,7-Heptanedial).
7. The method of claim 4 wherein the dialdehyde cross-linking reagent is glutaraldehyde.
8. The method of claim 1, wherein the multi-functional cross-linking reagent is used in a percent concentration of less than 2% (w/v).
9. The method of claim 8, wherein the multi-functional cross-linking reagent is used in a percent concentration of 0.5% or less (w/v).
10. The method of claim 9, wherein the multi-functional cross-linking reagent is used in a percent concentration of 0.2% or less (w/v).
11. The method of claim 1, wherein the polymer having one or more reactive moieties effective to adhere to the crystal layer is a polyamino acid, a polycarbohydrate, a polystyrene, a polyacid, a polyol, a polyvinyl, a polyester, a polyurethane, a polyolefin, or a polyether.
12. The method of claim 11, wherein the polymer having one or more reactive moieties effective to adhere to the crystal layer is a polyamino acid.

13. The method of claim 12, wherein the polyamino acid is a polylysine, a polyamide, a polyglutamic acid, a polyaspartic acid, a copolymer of lysine and alanine, or a copolymer of lysine and phenylalanine.
14. The method of claim 13, wherein the polyamino acid is polylysine.
15. The method of claim 14, wherein said enzyme is phenylalanine ammonia lyase.
16. The method of claim 14, wherein the multi-functional cross-linking reagent is used in a percent concentration of 0.5% or less (w/v).
17. The method of claim 16, wherein the multi-functional cross-linking reagent is used in a percent concentration of 0.2% or less (w/v).
18. Matrix stabilized enzyme crystals prepared according to the method of claim 1.
19. Matrix stabilized enzyme crystals prepared according to the method of claim 14.
20. Matrix stabilized enzyme crystals prepared according to the method of claim 15.
21. Matrix stabilized enzyme crystals of phenylalanine ammonia lyase comprising crystalline PAL cross-linked with a bifunctional cross-linking agent in the presence of polylysine.
22. The matrix stabilized enzyme crystals of claim 21, wherein said bifunctional cross-linking agent is glutaraldehyde.
23. A method of treating hyperphenylalaninemia comprising administering a therapeutically effective amount of matrix stabilized enzyme crystals of phenylalanine ammonia lyase.
24. The method of claim 23, wherein said matrix stabilized enzyme crystals of phenylalanine ammonia lyase are stabilized by cross-linking polylysine with phenylalanine ammonia lyase in the presence of less than 0.5% w/v bifunctional cross-linking agent.
25. The method of claim 24, wherein said bifunctional cross-linking agent is glutaraldehyde.
26. The method of claim 23, wherein the administration of matrix stabilized enzyme crystals of phenylalanine ammonia lyase is conducted by oral administration.